REMARKS

The Final Office action dated April 30, 2008, is acknowledged. Claims 1-21 and 27-43 are pending in the instant application. The Applicants wish to thank the Examiner for accepting the terminal disclaimers, and in turn withdrawing the double-patenting rejections. According to the Final Office action, each of these claims has been rejected. By the present Final Office Action response, claim 43 has been amended, in particular to clarify the recitation therein and to depend from claim 41 rather than claim 42. Support for the amendments to claim 42 may be found throughout the specification, such as at paragraphs [000012], [000030] and [000031]. The Examiner also states in the Office action (page 9) that the submitted PCT application is not in English and so the Examiner was unable to find the support for the newly added limitations submitted in the previous Office action response. A copy of the English translation of the PCT application is submitted herewith which provides support for the limitation "not combined with an acid," as well as the limitation "acid" in the present text rather than "salt." Paragraph [000017] has been amended to correspond with the English translation of the original application, namely, to include the limitation "Combined with an acid, but also without an acid..." (page 5, last paragraph, of the translation). Reconsideration is respectfully requested in light of the amendments being made hereby and the arguments made herein. No new matter has been added.

Rejection of claims 1-21 and 27-43 under 35 U.S.C. 112, first and second paragraphs

Claims 1-21 and 27-43 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the art that the inventors had possession of the invention. In particular, the Examiner states that the present specification does not support the limitation "carbon dioxide forming substance which is not combined with an acid." The Examiner further states that while the specification discloses that the preparation is capable of disintegrating slowly within a period of 3-15 minutes, it appears that the specification does not provide support for the limitations "preparation is not capable of disintegrating in an aqueous medium" (emphasis provided) and "removing the preparation from said oral mucosa after the active substance has been released" in claim 43. The Examiner argues that "slowly disintegrates" is not the same as "not capable of disintegrating."

Claim 43 has been rejected under 35 U.S.C. 112, second paragraph, for failing to further limit the subject matter of claim 42. In particular, the Examiner states that while claim 42 requires the preparation to disintegrate upon contact with oral mucosa, claim 43 recites that the preparation is not capable of disintegration. The Examiner has also rejected claim 43 due to the uncertainty of the meaning of the phrase "preparation is not capable of disintegrating in an aqueous medium."

The Applicants respectfully request that rejections under 35 U.S.C. 112 be withdrawn. Claim 43 has been amended to depend from claim 41 rather than 42 to provide proper further limitation thereof. In addition, claim 43 has been amended to recite a preparation which is "mucoadhesive but not capable of disintegrating," and the method step has been amended to recite the step "applying said preparation to the oral mucosa." These amendments are supported by the specification, such as at paragraphs [000012], [000030] and [000031].

The Examiner has also raised the issue as to whether the preparation of claim 43 would not disintegrate in the aqueous medium. As supported by paragraph [000030] of the present specification, the present invention includes preparations (or "systems") which do not disintegrate or erode. In this case, the active substance is released from the preparation essentially by diffusion processes, and finally the "empty" preparation which is still un-degraded has to be removed from the oral cavity.

Regarding the amendment of claim 1 set forth in the previous Office action response, namely, the limitation "not combined with an acid," a copy of the English translation of the PCT application is submitted herewith to support the limitation.

Withdrawal of these rejections is respectfully requested.

Rejection of claims 1-3, 5-12, 15-21, 29-31 and 33-41 under 35 U.S.C. 102(a) and 102(e)

Claims 1, 2, 5-12, 16, 17, 20, 21, 29-31, 35, 36 and 39-41 have been rejected under 35 U.S.C. 102(a) as being anticipated by WO 02/02085 (corresponding to U.S. Publication No. 2004/0028732) (Falkenhausen, et al.). The Examiner essentially concludes that Falkenhausen, et al. disclose every limitation recited in present claims 1, 2, 5-12, 16, 17, 20, 21, 29-31, 35, 36 and 39-41. In particular, the Examiner states that Falkenhausen, et al. teach a rapidly disintegrating sheet or wafer dosage form having a thickness of between 0.1-5 mm, the dosage form comprising matrix-forming polymers, active ingredients, and a carbon dioxide gas forming agent. The Examiner further states that the polymers include cellulosic polymers, and water-soluble polysaccharide. Lastly, the Examiner states that the dosage form further comprises eucalyptus oil, peppermint oil,

flavor, sweetener, other additives and foams, such as propylene glycol and that the dosage form disintegrates in the oral cavity in the range from 10-30 seconds.

Claims 1-3, 5-12, 15-21, 29-31 and 33-41 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Publication No. 2006/0057207 (Ziegler, et al.) As set forth on pages 4-5 of the Final Office action, the Examiner concludes that Ziegler, et al. disclose every limitation recited in these claims. In particular, the Examiner states that Ziegler, et al. disclose a fast disintegrating film or wafer comprising an active agent, film-forming polymers, effervescent disintegrants (i.e., gas-forming agent) and filler and that film-forming polymers are disclosed in paragraph [0076] of Ziegler, et al. The Examiner also states that Ziegler, et al. teach that the film-forming polymers are added in an amount that falls within the claimed range, e.g., 0.01 – 99% and that effervescent disintegrants include sodium carbonate. Furthermore, it is stated in the Office action that the film further comprises water, additional film-forming agent, plasticizing agent, flavoring, saliva stimulating agents, cooling agent, surfactant, stabilizing agent, emulsifying agent, thickening agents, binding agent, coloring agent, sweetening agent, fragrance and the like, and that Ziegler, et al. disclose that the film has a thickness that falls within the claimed range (i.e., between 30 μm to 300 μm). Lastly, the Examiner states that Ziegler, et al. disclose that the film disintegrates in a patient's oral cavity in less than one minute. The Examiner does point out that Ziegler, et al. fail to teach the claimed properties, such as the density, but that the density is inherent because Ziegler, et al. teach the use of the same polymer and the same carbon dioxide forming agent to obtain the same wafer composition having the claimed disintegrating time, and that this would be obvious to one skilled in the art.

The Applicants respectfully disagree with the Examiner's conclusion and submit that the present invention as defined in the present claims is patentably distinct from the inventions disclosed in both Falkenhausen, et al. and Ziegler, et al. In particular, the Applicants submit that, regarding claim 1 and the respective dependent claims, the Examiner has not taken into consideration the limitation of the present invention of "without an acid." Paragraph [0036] of Falkenhausen, et al. relates to the addition of gas-forming compounds during the manufacture, which – through chemical reaction of these compounds – results in a foamed composition. As these gas-forming compounds are merely used to cause foaming during production, Falkenhausen, et al. cannot be interpreted as teaching the presence of a carbon dioxide-forming substance in the final product. In particular, Falkenhausen, et al. clearly fail to disclose the presence of a carbon dioxide-forming substance which is not combined with an acid.

Turning now to Ziegler, et al., the Applicants reiterate the position that Ziegler, et al. is not a properly cited reference, as discussed in detail in the previous Office action response (page 13, Office action response filed January 28, 2008). As noted therein, Ziegler, et al. is a continuation-in-part application, and the passages relied upon in that reference by the Examiner are not supported by the parent application from which the CIP application was derived. In further support of this matter, enclosed herewith is a copy of a relevant page of US Publication No. 2003/0180360 which is the publication of U.S. Application No. 10/300,308 which formed the basis of Ziegler's CIP Application No. 11/270,766 and which is published as U.S. Publication No. 2006/0057207.

U.S. '360 relates to controlled-release (CR) oral dosage forms (emphasis added) but does not teach any effervescent agents. In the subsequent CIP application, additional

subject matter was included based on Provisional Application No. 60/642,083 which has a filing date of January 7, 2005 (a copy of the information page from the PAIR website is enclosed for ease of reference), which pertains to "Fast-disintegrating Dosage Forms." On page 10 of the provisional application, "effervescent excipients" are mentioned in connection with fast-disintegrating dosage forms and microparticles. The effervescent excipients promote the disintegration of the multiparticulate preparation (page 10, a copy of which is enclosed as well). The Applicants submit that the aforementioned subject matter was newly added in the Provisional Application No. 60/642,083 filed on January 7, 2005, and which is a date after the filing date of the present application.

As set forth in the previous Office action response, Ziegler, et al. is a continuation-in-part application (CIP) of Application Serial No. 10/300,608, which in turn is a non-provisional patent application based on provisional application Serial No. 60/334,652 (filed on November 30, 2001). At noted in the previous Office action response, this provisional application does not disclose effervescent disintegration agents, which were first introduced in the 10/300,608 application filed on November 20, 2002. This is a date after the February 21, 2002 priority date of the present application. In addition, the '608 application was published on September 25, 2003, which is not a date more than one year prior to the date of the application of the present application (i.e., August 20, 2004).

Therefore, it is respectfully submitted that Ziegler, et al. cannot be relied up as prior art and should be withdrawn. Withdrawal of the present rejection is respectfully requested.

Rejection of claims 1-21, 27-32 and 33-42 under 35 U.S.C. 103(a)

Claims 1-12, 15-21, 27-31 and 33-42 have been rejected as being unpatentable over Ziegler, et al. in view of U.S. Publication No. 2003/0091629 (Pather, et al.). The Examiner argues that Ziegler, et al. teach every limitation of these claims (as discussed above) but fail to teach the claimed amount of the gas-forming agent. The Examiner notes that Ziegler, et al. teach the use of saliva stimulating agent in an amount that falls within the claimed range (i.e., about 0.01% to about 12%) and that Ziegler, et al. disclose the use of sodium carbonate as an effervescent disintegration agent to stimulate saliva production, thereby providing additional water to aid in further effervescence and disintegration. The Examiner further argues that Pather, et al. teach an effervescing sublingual buccal dosage form comprising a drug, an additive, and an effervescent in an amount of about 5% to about 95%, as well as that the effervescent includes sodium carbonate and potassium carbonate. The Examiner concludes that it would have been obvious to one skilled in the art to modify the fast disintegrating dosage of Ziegler, et al. to include the carbonates in an amount in view of the teaching of Pather, et al. for arriving at the present invention. It is stated that this is because Pather, et al. teach the use of effervescent in an amount to influence the permeability of the medicament across the buccal, sublingual and gingival mucosa, because Ziegler, et al. teach the use of sodium carbonate in the dosage form, and because Ziegler, et al. teach the desirability to obtain a fast disintegrating dosage form useful for buccal and sublingual delivery.

Claims 1-12, 16, 17, 19-21, 27-31, 35, 36 and 39-42 have been rejected as being unpatentable over Falkenhausen, et al. in view of Pather, et al. As noted in the Office action on pages 6-7, the Examiner argues that Falkenhausen, et al. teach every limitation of these claims (as discussed earlier) except for the carbon dioxide forming substance.

The Examiner relies on Pather, et al. for this missing teaching of Falkenhausen, et al., in particular an effervescing sublingual buccal dosage form comprising a drug, an additive and an effervescent in an amount of about 5% to about 95%, as well as effervescent includes sodium carbonate and potassium carbonate. The Examiner concludes that it would have been obvious to one skilled in the art to modify the rapidly disintegrating dosage of Falkenhausen, et al. to include the carbon dioxide forming substance, such as sodium carbonate, in an amount in view of the teaching of Pather, et al. for arriving at the present invention. It is stated that this is because Pather, et al. teach the use of effervescent in an amount so as to influence the permeability of the medicament across the buccal, sublingual and gingival mucosa, because Pather, et al. teach the use of sodium carbonate to evolve gas such as carbon dioxide gas, and because Falkenhausen, et al. teach the desirability of using carbon dioxide gas forming substance.

The Examiner does note that Falkenhausen, et al. also fail to teach the amount of water-soluble polymer, but that differences in concentration will not support patentability unless there is evidence indicating such concentration is critical. Thus, it is concluded that it would have been obvious to one of ordinary skill in the art to, by routine experimentation, select an amount of matrix-forming polymer that falls within the claimed range since Falkenhausen, et al. disclose the desirability to use the same matrix-forming polymer to obtain the same film shape dosage form having the same disintegrating time.

Claim 32 has been rejected as being unpatentable over Ziegler, et al. or Falkenhausen, et al. in view of U.S. Publication No. 2007/0122455 (Myers, et al.). As noted in the Office action on pages 7-8, the Examiner argues that Ziegler, et al. or

Falkenhausen, et al. fail to teach ethyl cellulose as a film-forming polymer. The Examiner in turn relies on Myers, et al. for this missing teaching of Ziegler, et al. or Falkenhausen, et al. and concludes that it would have been obvious to one skilled in the art to have modified the rapidly disintegrating dosage of Ziegler, et al. or Falkenhausen, et al. using ethyl cellulose as a film-forming polymer in view of the teaching of Myers, et al. because Myers, et al. teach using ethyl cellulose in rapid-dissolve film-shaped dosage form is well known in the art and since both Ziegler, et al. or Falkenhausen, et al. teach the desirability for using cellulosic film-forming polymers.

Claims 13 and 14 have been rejected as being unpatentable over Ziegler, et al. in view of U.S. Patent No. 5,800,832 (Tapolsky, et al.). The Examiner states in the Office action that Ziegler, et al. fail to teach the film layers as claimed in claims 13 and 14. However, the Examiner relies on Tapolsky, et al. for this missing limitation and concludes that it would have been obvious to one skilled in the art to have combined the teachings of these references to arrive at the presently claimed invention as set forth in claims 13 and 14. In particular, the Examiner states that Tapolsky, et al. teach a water-soluble, bioerodable delivery device comprising an adhesive layer and a non-adhesive backing layer and that the two layers have different dissolution rate. Thus, the Examiner concludes that it would have been obvious to modify the delivery thin film of Ziegler, et al. to contain the mucoadhesive bioerodable film in view of the teaching of Tapolsky, et al. because Tapolsky, et al. teach a mucoadhesive bioerodable film provides adhesive to mucosal surface with minimal discomfort and ease of use, because Tapolsky, et al. teach using mucoadhesive to maintain the delivery device at the site of treatment, and because Ziegler, et al. teach the thin film delivery system includes multi-layer system.

The Applicants respectfully submit that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all of the claim limitation. The Applicants respectfully submit that one skilled in the art would have no suggestion or motivation to combine the aforementioned references in order to arrive at the present invention. Additionally, even if one skilled in the art were to consider the teachings of the cited prior art alone, or in combination, each and every limitation of the present invention would not be disclosed, nor would there be a reasonable expectation of success if the aforementioned references were to be considered. In addition, prior art must be considered in its entirety, i.e., as a whole (emphasis provided), including portions that would lead away from the claimed invention (M.P.E.P. §2141.02, citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220, USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)), proposed modification cannot render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference (M.P.E.P. §2143.01), and Examiner's conclusion of obviousness may not be based on improper hindsight (M.P.E.P. §2145(X)(A)).

The Applicants first submit that the present invention is based on the unexpected finding that in the case of flat-shaped or wafer-shaped oral administration forms, it is possible to mask or suppress the bitter taste of a medicinal substance which is present in such an administration form, by incorporating a carbon-dioxide forming substance. Surprisingly, the taste-masking effect is observed even when the carbon dioxide-forming

substance is not combined with an acidic component (specification, paragraph [000017]) as would be required in accordance with prior art practice. In other words, the taste-masking effect is not dependent on adding an acidic component. Due to these reasons, the presently claimed compositions are also advantageous with respect to the manufacturing process since they can be produced from an aqueous solution rather than from hot-melts. It is submitted that when using "effervescent couples" (i.e., carbon dioxide-forming substance combined with an acid) as taught in the prior art, hot-melts or non-aqueous solutions are generally required to avoid premature gas formation.

The Applicants first respectfully disagree with the Examiner's opinions for at least the reasons set forth above regarding Ziegler, et al., in particular since Ziegler, et al. should be withdrawn from consideration as prior art. Moreover, as discussed in the previous Office action response, Ziegler, et al. merely teach the combined use of an effervescent substance with an acid (paragraph [0048] of Ziegler, et al.). Notwithstanding the aforementioned issues regarding Ziegler, et al., the combination of teachings of Ziegler, et al. and Pather, et al. fail to teach each and every limitation of the presently claimed invention. Pather, et al. will be addressed further below.

Turning now to Falkenhausen, et al., as discussed above, the reference teaches adding gas-forming substances during production in order to obtain foamed dosage forms. Therefore, according to Falkenhausen, et al., the final product is obtained when the gas-forming reaction is completed and the preparation is solidified to maintain the foam structure (e.g., paragraph [0036] of Falkenhausen, et al.). Since the gas formation process is already completed at the end of the manufacturing process, it cannot be assumed that the resulting product (i.e., the dosage form) would still contain any gas-

forming excipients. Although claim 11 of Falkenhausen, et al. recites the presence of gas-forming excipients enclosed within the cavities of the matrix, it is submitted that the recitation does not imply the presence of a carbon dioxide-forming substance in the absence of an acid (which would be required for gas formation).

In the Response to Arguments section of the Final Office action (page 10, lines 11-12), the Examiner notes that "the process recited in the claims of Falkenhausen, et al. does not require the addition of the acid." However, it is respectfully submitted that in general, failure to recite an element in a claim does not necessarily indicate that the element would not be required. Claims 12 and 15 of Falkenhausen, et al., in step (b), recite "chemical production of gas." It is respectfully submitted that it would be readily clear to one skilled in the art that the addition of an acidic component will have to be combined with a carbon dioxide-forming compound in order to achieve "chemical production of gas."

Turning now to Pather, et al., the reference teaches using effervescent agents as penetration enhancers. However, in accordance with the other prior art, the Pather, et al. reference assumes that carbon dioxide-forming substances must be combined with acids. According to Pather, et al., the penetration-enhancing effect is due to the effervescent effect of the effervescent agents. However, in the case of carbon dioxide-forming substances, such as sodium bicarbonate, the addition of an acid is required in order to start and maintain the gas-forming reaction (see the Examples of Pather, et al.). Since, according to the teaching of Pather, et al., it is considered essential to produce an effervescent effect, and since carbon dioxide-forming substances must be combined with acids to support gas production, Pather, et al. could not have suggested adding a carbon

dioxide-forming substance which is not combined with an acid (see, for example, paragraphs [0015] – [0017]; [0019] and [0022]). Likewise, Falkenhausen, et al. teach adding carbon dioxide-forming substances for product an effervescent (bubbling) effect which is required to produce a foamed matrix.

Therefore, Falkenhausen, et al. when combined with Pather, et al. fail to teach or suggest adding a carbon dioxide-forming agent without an acid. It is respectfully submitted that it would therefore not be obvious to one skilled in the art to have combined said teachings to arrive at the presently claimed invention, and that such combination would still fail to teach every presently claimed limitation. Therefore, withdrawal of this rejection is respectfully requested.

Regarding the rejection of claim 32 as being unpatentable over Ziegler, et al. or Falkenhausen, et al. in view of Myers, et al., the Applicants respectfully traverse for at least the numerous deficiencies of Ziegler, et al. and Falkenhausen, et al., discussed above. Moreover, Myers, et al. was cited merely for teaching ethyl cellulose as a film-forming polymer and the reference fails to make up for the aforementioned deficiencies of Ziegler, et al. and Falkenhausen, et al. Therefore, it is respectfully submitted that this rejection be withdrawn.

Regarding the rejection of claims 13-14 as being unpatentable over Ziegler, et al. in view of Tapolsky, et al., the Applicants respectfully traverse for at least the various deficiencies of Ziegler, et al., discussed above. Moreover, Tapolsky, et al. was cited merely for teaching a bilayer comprising a non-mucoadhesive layer and the reference fails to make up for the deficiencies of Ziegler, et al. Therefore, it is respectfully submitted that this rejection be withdrawn.

It is therefore respectfully submitted that the present invention defined in the presently amended claims is patentably distinguishable over the combination of prior art teachings under 35 U.S.C. 103(a). Based on the aforementioned differences, each and every element of the present invention recited in the instant claims are not taught or disclosed in the prior art references, alone or in combination. Moreover, one skilled in the art would not be motivated to combine the teachings of said references or to modify the cited prior art references to arrive at the presently claimed invention, and the cited prior art references teach away from the present invention. Therefore, the Applicants respectfully request that these obviousness rejections be withdrawn.

Conclusion

For the foregoing reasons, it is believed that the present application, as amended, is in condition for allowance, and such action is earnestly solicited. Based on the foregoing arguments, amendments to the claims and deficiencies of the prior art references, the Applicants strongly urge that the obviousness-type rejection and anticipation rejections be withdrawn. The Examiner is invited to call the undersigned if there are any remaining issues to be discussed which could expedite the prosecution of the present application.

Respectfully submitted,

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but other physiologically acceptable carbon dioxide-forming substances may also be utilized. Preferred carbon dioxide-releasing substances are sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate or potassium carbonate. Carbon dioxide-forming substances are known to those skilled in the art and may be effective when combined with each other.

The sensation of taste in the case of oral application of a pharmaceutical preparation according to the present invention which contains a carbon dioxide-forming substance without added salt is, surprisingly, altered such that bitter-tasting substances or active agents do no longer produce this unpleasant sensation of taste, or do so only to a strongly reduced degree.

The pharmaceutical preparations according to the present invention are suitable for a plurality of different active substances.

AMENDED CLAIMS

1. Film-shaped or wafer-shaped pharmaceutical preparation for administering active substances, said preparation containing at least one matrix-forming polymer which has at least one active substance and at least one gas-forming component dissolved or dispersed therein, characterized in that the said gas-forming component consists of a carbon dioxide-forming substance or of a combination of such substances, and reduces or completely suppresses an unpleasant taste sensation caused by the active substance.

2. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 1, characterized in that said pharmaceutical preparation is suitable for administration of active substance(s) via the oral mucosa.

3. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 1 or 2, characterized in that the carbon dioxide-forming substance or at least one of the carbon dioxide-forming substances is/are selected from the group consisting of sodium hydrogencarbonate, sodium carbonate, potassium carbonate and potassium hydrogen carbonate.

4. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that the carbon dioxide-forming substance is contained in the pharmaceutical preparation in an amount of 2 to 50%-wt, preferably 5 to 30%-wt, and with particular preference 7 to 20%-wt, relative to the pharmaceutical preparation.

5. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized

in that it contains at least one permeation enhancer and/or at least one substance stimulating the blood flow.

6. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 5, characterized in that the permeation enhancer is selected from the group consisting of saturated or unsaturated fatty acids, hydrocarbons, straight-chain or branched fatty alcohols, dimethyl sulfoxide, propylene glycol, decanol, dodecanol, 2-octyldodecanol, glycerol, isopropylidene glycerol, transcutol (= diethyleneglycol-monoethyl ether), DEET (= N,N-diethyl-m-tolueneamide), solketal, ethanol or other alcohols, menthol and other essential oils or components of essential oils, lauric acid diethanolamide, D-alpha-tocopherol and dexpanthenol.

7. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 5, characterized in that the substance stimulating the blood flow is selected from the group consisting of menthol, eucalyptol, ginkgo extract, geranium oil, camphor, spearmint oil, oil of juniper, and rosemary.

8. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that it disintegrates within 15 min, preferably within 3 min, and particularly preferably within 60 seconds, after introduction into an aqueous medium.

9. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that the matrix-forming polymer(s) is/are selected from the group consisting of polyvinyl alcohol, cellulose derivatives, starch and starch derivatives, gelatine, polyvinyl pyrrolidone, gum arabic, pullulan, acrylates, polyethylene oxide, and copolymers of methyl vinyl ether and maleic acid anhydride, with the group of the cellulose derivatives preferably consisting of hydroxypropylmethyl cel-

lulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose and hydroxypropylethyl cellulose.

10. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of claims 1 to 7, characterized in that the matrix-forming polymer(s) is/are selected from the group consisting of cellulose ether, preferably ethyl cellulose, as well as polyvinyl alcohol, polyurethane, polymethacrylate, polymethyl methacrylate, and derivatives and copolymerisates of the aforementioned polymers.

11. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that the pharmaceutical preparation contains an auxiliary substance imparting mucoadhesive properties to the preparation.

12. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 11, characterized in that the auxiliary substance is selected from the group consisting of polyacrylic acid, carboxymethyl cellulose, hydroxymethyl cellulose, methyl cellulose, tragacanth, alginic acid, gelatine and gum arabic, or a mixture thereof.

13. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 11, characterized in that the pharmaceutical preparation has a bilayer or multilayer structure, with only the layer or layers which is/are facing the oral mucosa, respectively which is/are in contact with the oral mucosa, being rendered mucoadhesive.

14. Film-shaped or wafer-shaped pharmaceutical preparation according to claim 13, characterized in that the non-mucoadhesive layers have a lower permeability for the active substance, respectively the active substances.

15. Film-shaped or wafer-shaped pharmaceutical preparation according to any of the preceding claims, characterized in that it is flat-shaped, with the thickness of this flat-shaped preparation preferably lying between 0.3 g/cm³ and 1.7 g/cm³, with particular preference between 0.5 g/cm³ and 1.5 g/cm³, and most preferably between 0.7 g/cm³ and 1.3 g/cm³.

16. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that its total thickness is 5 µm to 10 mm, preferably 30 µm to 2 mm, and with particular preference 0.1 mm to 1 mm.

17. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that it has a round or ellipsoid or oval shape, or a triangular, quadrangular or polygonal shape, or an irregular rounded shape.

18. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that it is present as a solidified foam, the density of this solidified foams preferably being between 0.01 g/cm³ and 0.8 g/cm³, with particular preference between 0.08 g/cm³ and 0.4 g/cm³, and with greatest preference between 0.1 g/cm³ and 0.3 g/cm³.

19. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that the polymer portion of the matrix amounts to at least 3%-wt. and maximally 98%-wt., preferably 7 to 80%-wt., with particular preference 20 to 50%-wt., each value being relative to the entire preparation.

20. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that it contains at least one auxiliary substance, said auxiliary substance(s) being selected from the group consisting of fillers, colourants, disintegrants, emulsifiers, plasticizers, sweeteners, preserving agents, stabilisers, antioxidants and flavouring agents.

21. Film-shaped or wafer-shaped pharmaceutical preparation according to any one of the preceding claims, characterized in that it contains at least one flavouring agent and/or at least one sweetener and/or at least one plasticizer.

22. Use of the film-shaped or wafer-shaped pharmaceutical preparation according to any one of claims 1 to 21 for administration of active substance(s), preferably at least one active substance which has a bitter taste.

23. Use of the film-shaped or wafer-shaped pharmaceutical preparation according to any one of claims 1 to 21 for administration of active substance(s) to an oral mucosa of a human or animal organism, preferably for oral administration.

24. Process for oral administration of pharmaceutically active substance(s) having a bitter taste, characterized by applying a film-shaped or wafer-shaped pharmaceutical preparation according to any one of claims 1 to 21.

25. Process according to claim 24, characterized by applying pharmaceutical preparations which are capable of disintegrating in aqueous media.

26. Process according to claim 24 or 25, characterized by applying a mucoadhesive pharmaceutical preparation to the surface of the oral mucosa of said organism.

US 20030180360A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0180360 A1

Am Ende et al. (43) Pub. Date: Sep. 25, 2003

(54) PHARMACEUTICAL COMPOSITIONS OF 5,7,14-TRIAZATETRACYCLO[10.3.1.02,11.04,9]-HEXADECA-2 (11),3,5,7,9-PENTAENE

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(21) Appl. No.: 10/300,608

(22) Filed: Nov. 20, 2002

Related U.S. Application Data

(60) Provisional application No. 60/334,652, filed on Nov. 30, 2001.

Publication Classification

(51) Int. Cl.[7] A61K 31/33; A61K 9/22; A61K 9/14

(52) U.S. Cl. 424/468; 514/183

(57) ABSTRACT

The present invention is directed to controlled-release (CR) oral pharmaceutical dosage forms of 5,8,14-triazatetracyclo [10.3.1.0^{2,11}.0^{4,9}]-hexadeca-2(11),3,5,7,9-pentaene, 1, and pharmaceutically acceptable salts thereof, and methods of using them to reduce nicotine addiction or aiding in the cessation or lessening of tobacco use while reducing nausea as an adverse effect. The present invention also relates to an immediate-release (IR) low dosage composition having a stable formulation with uniform drug distribution and potency.

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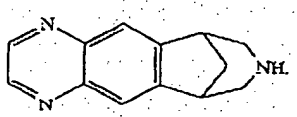

are described in G. Santus and R. W. Baker, *J. Control. Rel.*, 1995, 35, 1-21, incorporated herein by reference. Other single-layer osmotic tablets are described in copending application PC11850, incorporated herein by reference. A particularly preferred osmotic dosage form for 1 is in the form of an AMT system, as described for example in U.S. Pat. Nos. 5,612,059 and 5,698,220. (See, also, S. M. Herbig, *J. Control. Rel.*, 1995, 35, 127-136). Such systems provide for good control of the drug release throughout the GI system. The inventors have found that preferred formulations consist of cores made from the L-tartrate salt of the drug, mannitol, microcrystalline cellulose, dicalcium phosphate and magnesium stearate. These cores can be prepared by direct compression, wet granulation (with a high or low shear wet granulator or fluid bed granulator), extrusion granulation, rotogranulation or roller compaction. Roller compaction is especially preferred due to its ability to prevent drug segregation, while maintaining drug stability (in contrast to aqueous wet granulations which can lead to drug hydrate formation). The tablets can be prepared on standard tablet presses (rotary). The tablet cores are then coated using a pan coater. The coating favorably consists of a mixture of cellulose acetate (CA) and polyethylene glycol (PEG) coated from acetone and water. The ratio of components is selected such that the CA/PEG combination produce a porous, semipermeable coating which administers the drug through the pores in the GI tract at the desired rate. Most preferably, the ratio of CA to PEG is chosen such that the PEG is in a single phase with the CA since phase-separated PEG was found to lead to drug degradation at elevated temperatures in the final dosage form. Phase compatibility for the purpose of this invention can be determined using a standard differential scanning calorimeter on the desired CA to PEG blend. The absence of a PEG melt transition between 30° C. and 50° C. is an indication of a single phase, and therefore, an indication that such a ratio will form a preferred film. It is therefore most preferred that the CA/PEG ratio remain above about 4.

[0051] Non-oral CR systems can also provide nausea reduction while maintaining efficacy upon administration of 1. These systems include suppositories, transdermal systems, buccal systems, depots and implantable devices. In order to function to reduce nausea, these devices must provide controlled-release behavior as described previously. A particularly preferred non-oral dosage form is a transdermal dosage form.

[0052] With all the CR dosage forms, the drug is preferably delivered at a rate of between about 0.06 and 3 mgA/hr; and more preferably between 0.1 and 1 mgA/hr. Suitability for the present invention can be determined either by in vivo or in vitro testing. In particular, it is preferred that the average initial C_{max} be reduced to achieve a value of 10 to 80% of that achieved with an average initial IR bolus administration; more preferred is between 30 and 70%. For T_{max}, an increase in the average initial T_{max} for a CR dosage form compared to an average initial IR bolus is preferred to be at least 50%. Preferred dosage forms for the present invention provide 50% w:w of the total dose into solution between about 1 and 15 hours; more preferably between 2 and 10 hours.

[0053] CR systems for the present invention can involve a delay or lag period between when the dose is administered and when drug is available for absorption. Such delays can be temporal or related to the position in the gastrointestinal tract. These systems will be effective for the purposes of the present invention as long as once they begin providing drug for absorption, the rate falls within the limits described above. A particularly preferred delayed release system is an enteric-coated tablet or multiparticulate. Preferred enteric systems can be prepared by coating tablets or multiparticulates with such materials as cellulose acetate phthalate or enteric polyacrylics such as those marketed under the Eudragit brand name (available from Rohm Pharmaceuticals).

[0054] Formulations useful for the present invention can be prepared using a wide range of materials and processes known in the art. The inventors have found, however, that the presence of reducing carbohydrates is detrimental to the drug stability on storage. In particular, CR formulations with less than 20% w/w of reducing carbohydrates are preferred; still more preferred are CR formulations with less than 10% w/w reducing carbohydrates; and most preferred are CR formulations with less than 5% w/w reducing carbohydrates. A particular reducing carbohydrate that is preferably avoided is lactose.

[0055] For preparation of the controlled release and immediate release dosage forms, the active ingredient may be used per se or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The active ingredient may be used per se or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "pharmaceutically acceptable salt" refers to non-toxic acid addition salts derived from inorganic and organic acids. Suitable salt derivatives include halides, thiocyanates, sulfates, bisulfates, sulfites, bisulfites, arylsulfonates, alkylsulfates, phosphonates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphonates, alkanoates, cycloalkylalkanoates, arylalkonates, adipates, alginates, aspartates, benzoates, fumarates, glucoheptanoates, glycerophosphates, lactates, maleates, nicotinates, oxalates, palmitates, pectinates, picrates, pivalates, succinates, tartarates, citrates, camphorates, camphorsulfonates, digluconates, trifluoroacetates, and the like.

[0056] The final pharmaceutical composition is processed into a unit dosage form (e.g., tablet, capsule or sachet) and then packaged for distribution. The processing step will vary depending upon the particular unit dosage form. For example, a tablet is generally compressed under pressure into a desired shape and a capsule or sachet employs a simple fill operation. Those skilled in the art are well aware of the procedures used for manufacturing the various unit dosage forms.

[0057] The active blend of an immediate release dosage form generally includes one or more pharmaceutically acceptable excipients, carriers or diluents. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the active ingredient is being applied. In general, an immediate release tablet formulation includes materials such as diluents, binders, lubricants, glidants, disintegrants and mixtures thereof. Although many such excipients are known to those skilled in the art, the inventors have found that only a sub-set of those provide for the most stable formulations. In particular, the inventors have found that preferred formulations contain less than about 20% w:w reducing carbohydrates. Reducing carbohydrates are sugars

and their derivatives that contain a free aldehyde or ketone group capable of acting as a reducing agent through the donation of electrons. Examples of reducing carbohydrates include monosaccharides and disaccharides and more specifically include lactose, glucose, fructose, maltose and other similar sugars. The inventors have further found that formulations containing dicalcium phosphate are particularly stable. More specifically, stable formulations are produced with more than about 20% w:w dicalcium phosphate. Other acceptable excipients include starch, mannitol, kaolin, calcium sulfate, inorganic salts (e.g., sodium chloride), powdered cellulose derivatives, tribasic calcium phosphate, calcium sulfate, magnesium carbonate, magnesium oxide, poloxamers such as polyethylene oxide and hydroxypropyl methylcellulose. To ensure content uniformity of the blend, a volume mean diameter drug substance particle size of less than or equal to about 30 microns is preferably utilized. Preferred diluents are microcrystalline cellulose (e.g., Avicel® PH200, PH102 or PH101 available from FMC Pharmaceutical, Philadelphia, Pa.) and calcium phosphate dibasic, or dicalcium phosphate, (e.g. A-Tab® available from Rhodia, Chicago Heights, Ill.). The mean particle size for the microcrystalline cellulose generally ranges from about 90 μm to about 200 μm. Suitable grades of dicalcium phosphate include anhydrous (about 135 to 180 pm mean, available from PenWest Pharmaceuticals Co., Patterson, N.Y. or Rhodia, Cranbury, N.J.), and dihydrate (about 180 μm, available from PenWest Pharmaceuticals Co., Patterson, N.Y. or Rhodia, Cranbury, N.J.). Generally, the microcrystalline cellulose is present in an amount from about 10 wt % to about 70 wt % and the dicalcium phosphate is present in an amount from about 10 wt % to about 50 wt %, more preferably, microcrystalline cellulose is present in an amount of about 30-70 wt % and the dicalcium phosphate is present in an amount of about 20-40 wt %.

[0058] If desired, a binder may be added. Suitable binders include substances such as celluloses (e.g., cellulose, methylcellulose, ethylcellulose, hydroxypropyl cellulose and hydroxymethylcellulose), polypropylpyrrolidone, polyvinylpirrolidone, gelatin, gum arabic, polyethylene glycol, starch, natural and synthetic gums (e.g., acacia, alginates, and gum arabic) and waxes.

[0059] A lubricant is typically used in a tablet formulation to prevent the tablet and punches from sticking in the die. Suitable lubricants include calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated vegetable oil, light mineral oil, magnesium stearate, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate. A preferred lubricant is magnesium stearate. The magnesium stearate is generally present in an amount from about 0.25 wt % to about 4.0% wt %.

[0060] Disintegrants may also be added to the composition to break up the dosage form and release the compound. Suitable disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, powdered cellulose, lower alkyl-substituted hydroxypropyl cellulose, polacrilin potassium, starch, pregelatinized starch and sodium alginate. Of these, croscarmellose sodium and sodium starch glycolate are preferred, with croscarmellose sodium being most preferred. The croscarmellose sodium is generally present in an amount from about 0.5 wt % to about 6.0 wt %. The amount of disintegrant included in the dosage form will depend on several factors, including the properties of the dispersion, the properties of the porosigen (discussed below), and the properties of the disintegrant selected. Generally, the disintegrant will comprise from 1 wt % to 15 wt %, preferably from 1 wt % to 10 wt % of the dosage form.

[0061] Examples of glidants include silicon dioxide, talc and cornstarch.

[0062] A film coating on the immediate release dosage form can provide ease of swallowing, reduction in unpleasant taste or odor during administration, improved photostability through use of an opacifier, improved elegance, reduced friction during high-speed packaging, or as a barrier between incompatible substances (G. Cole, J. Hogan, and M. Aulton, *Pharmaceutical Coating Technology*, Taylor and Francis Ltd, Ch 1, 1995). When used, the inventors have found that coatings containing a majority of cellulosic polymers provide superior chemical stability for the drug. Cellulosics are polymers derived from cellulose. Examples of polymers include cellulosics such as hydroxypropyl methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, methylhydroxyethylcellulose, methylcellulose, and sodium carboxymethylcellulose. A preferred polymer is hydroxypropyl methylcellulose. Coatings of the present invention comprise a polymer, an opacifier, a plasticizer a pharmaceutically acceptable diluent/filler and optionally acolorant. An opacifier is an excipient that help decrease the transmission of light through the coating to the core of the tablet. Examples of opacifiers include titanium dioxide and talc. A preferred opacifier is titanium dioxide. A plasticizer is a material which lower the glass transition temperature of the polymer thereby typically improving physical properties. Examples of plasticizers include polyhydric alcohols such as glycerol and polyethylene glycols and acetate esters such as glyceryl triacetate (triacetin) and triethyl citrate. Optionally, the compositions of the present invention may include a colorant. Such colorants are available from a number of commercial vendors and are well known to those skilled in the art. Particularly preferred coating formulations comprise HPMC, triacetin and titanium dioxide or HPMC, PEG and titanium dioxide.

[0063] To achieve a uniform distribution of drug in a blend prior to tablet or capsule production, two methods have been invented. In the first method, a geometric dilution process is used. In this process, a pre-blend of the drug and a portion of the excipients is prepared and subsequently further diluted with the remaining excipients in 2-5 additional steps. In the first dilution step, drug is mixed with 10-30 wt % of the excipient(s). In the second dilution, the first pre-blend is further diluted with 10-40 wt % excipient(s). In the third to fifth dilutions, the second dilution blend is further diluted with 10-75 wt % excipient(s) to form the final blend. A preferred dilution scheme involves first diluting the drug with the dicalcium phosphate in two increments, then combining with a blend of the remaining excipients.

[0064] The second process for achieving uniform drug distribution involves blending the formulation with a particular level of shear. The inventors have found unexpectedly that shear the is too high or low results in poor uniformity or total potency. The inventors have found that the desirable shear is achieved using either a bin blender or

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60/642,083 — **Fast-disintegrating dosage forms of 5,8,14-triazatetracyclo[10.3.1.02,11.04,9]-hexadeca-2(11),3,5,7,9-pentaene**

Application Data

Bibliographic Data

Application Number:	60/642,083	Customer Number:	-
Filing or 371 (c) Date:	01-07-2005	Status:	Provisional Application Expired
Application Type:	Provisional	Status Date:	01-08-2006
Examiner Name:	-	Location:	ELECTRONIC
Group Art Unit:	-	Location Date:	-
Confirmation Number:	2059	Earliest Publication No:	-
Attorney Docket Number:	PC32346	Earliest Publication Date:	-
Class / Subclass:	-	Patent Number:	-
First Named Inventor:	Carl Ziegler , East Lyme, CT (US)	Issue Date of Patent:	-

Title of Invention:	Fast-disintegrating dosage forms of 5,8,14-triazatetracyclo[10.3.1.02,11.04,9]-hexadeca-2(11),3,5,7,9-pentaene

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Application Data Sheet

Application Information

Application Type::	Provisional
Subject Matter::	Utility
Title::	FAST-DISINTEGRATING DOSAGE FORMS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.02,11.04,9]-HEXADECA-2(11),3,5,7,9-PENTAENE
Attorney Docket Number::	PC32346

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PC 32346

FAST-DISINTEGRATING DOSAGE FORMS OF 5,8,14-TRIAZATETRACYCLO[10.3.1.$0^{2,11}$.$0^{4,9}$]-HEXADECA-2(11),3,5,7,9-PENTAENE

CROSS REFERENCE TO RELATED APPLICATIONS

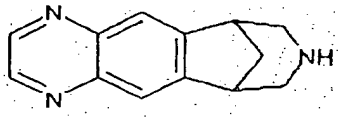
The present application is a continuation-in-part of Serial No. 10/300,608, filed Nov. 20, 2002, which claims the benefit of Serial No. 60/334,652, filed Nov. 30, 2001, which is incorporated herein by reference in its entirety.

1. Field of the Invention

The present invention relates to pharmaceutical compositions for medicinal uses thereof.

2. Background Art

Varenicline has the structure:



Varenicline is also known as 5,8,14-triazatetracyclo[10.3.1.$0^{2,11}$.$0^{4,9}$]-hexadeca-2(11),3,5,7,9-pentaene or 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]-benzazepine. Varenicline and pharmaceutically acceptable acid addition salts thereof are referred to in PCT International Patent Publication No. WO 99/35131, published July 15, 1999, the contents of which are incorporated herein by reference.

Varenicline binds to neuronal nicotinic acetylcholine specific receptor sites and are useful in modulating cholinergic function. Accordingly, this compound is useful in the treatment of various conditions or diseases including, but not limited to, inflammatory bowel disease (including, but not limited to, ulcerative colitis, pyoderma gangrenosum and Crohn's disease), irritable bowel syndrome, spastic dystonia, chronic pain, acute pain, celiac sprue, pouchitis, vasoconstriction, anxiety, panic disorder, depression, bipolar disorder, autism, sleep disorders, jet lag, amyotrophic lateral sclerosis (ALS), cognitive dysfunction, hypertension, bulimia, anorexia, obesity, cardiac arrhythmias, gastric acid hypersecretion, ulcers, pheochromocytoma, progressive supranuclear palsy, chemical dependencies and addictions (e.g., dependencies on, or addictions to nicotine (and/or tobacco products), alcohol, benzodiazepines, barbiturates, opioids or cocaine), headache, migraine, stroke, traumatic brain injury (TBI), obsessive-compulsive disorder (OCD), psychosis, Huntington's chorea, tardive dyskinesia, hyperkinesia, dyslexia, schizophrenia, multi-infarct dementia, age-related cognitive decline, epilepsy, including petit mal absence epilepsy, senile dementia of the Alzheimer's type (AD), Parkinson's disease (PD), attention deficit hyperactivity disorder (ADHD) and Tourette's Syndrome.

Varenicline is a highly potent compound such that dosage forms are necessarily highly diluted with excipients. The excipients provide dosage forms with adequate stability, while also providing for

the varenicline into a dosage form. These processing operations include drying, granulation, milling, compression, and the like.

In another embodiment of the present invention, effervescent excipients are incorporated into a varenicline solid dosage form. Once the dosage form is placed in the patient's oral cavity, contact with saliva promotes the acid-base reaction leading to rapid disintegration and release of the active varenicline. The effervescent sensation is not only pleasant to the patient, but also tends to stimulate saliva production, thereby providing additional water to aid in further effervescence and disintegration. Thus, once the dosage form (usually a tablet) is placed in the patient's mouth, it can disintegrate rapidly and completely without any voluntary action by the patient. Even if the patient does not chew the tablet, disintegration proceeds rapidly. Upon disintegration of the tablet, the active varenicline is released and can be swallowed as a slurry or suspension or it can dissolve in the saliva prior to swallowing. The varenicline can be in the form of a powder or it can be in microparticulate form with one or more excipients. The drug in microparticulate form is the preferred form as optionally it aids in taste-masking.

It is also preferred that the microparticles do not release the active varenicline in the oral cavity. Thus the varenicline can be transferred to the patient's stomach for dissolution in the digestive tract and systemic distribution of the pharmaceutical ingredient. In this way, the dosage form provides taste-masking.

The combination of the effervescent disintegration agent and the microparticles containing the varenicline provides an effective dosage form for systemic distribution. The microparticles can be relatively fragile microparticles susceptible to release of the pharmaceutical ingredient upon rupture of the microparticle. The tablet can disintegrate with minimal or no chewing, thus minimizing the problem of microparticle rupture. The effervescent disintegration agent includes any compound that evolves gas. The preferred effervescent agents evolve gas by chemical reactions that take place upon exposure of the effervescent disintegration agent to water and/or to saliva in the mouth. The bubble or gas generating reaction is most often the result of the reaction of a soluble acid source such as citric acid and an alkali metal carbonate or carbonate source such as sodium bicarbonate and sodium carbonate. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with water included in saliva. The dosage form according to this aspect of the present invention can further include one or more additional excipients including flavors, diluents, colors, binders, fillers, and non-effervescent disintegrants and can be chosen from those herein described.

When varenicline is present in microparticles, the microparticle can be provided as a microcapsule or as a matrix-type microparticle. Microcapsules typically incorporate a discrete mass of the pharmaceutical ingredient surrounded by a discrete, separately observable coating of the protective material. Conversely, in a matrix-type particle, the pharmaceutical ingredient is dissolved or suspended throughout the protective material. Certain microparticles can include attributes of both